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09/877,681	06/08/2001	Yihong Qiu	6437USP4	9430

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PAUL D. YASGER
ABBOTT LABORATORIES
100 ABBOTT PARK ROAD
DEPT. 377/AP6A
ABBOTT PARK, IL 60064-6008

EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
03/13/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_Abbott_Park@abbott.com
Legal_Patents@abbott.com

Office Action Summary	Application No.	Applicant(s)	
	09/877,681	QIU ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9,11 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,12-15 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The receipt is acknowledged of applicants' amendment filed 12/21/2007.

Claims 1-21 are pending.

Response to Election/Restrictions

1. This application contains claims 9, 11, and 16 drawn to an invention nonelected with traverse in the reply filed on 03/24/2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-8, 10, 12-15, and 17-21 are include din the prosecution.

The following rejections have been overcome by virtue of applicants' amendment and remarks:

(a) The rejection of claims 1-8, 10, 12-15, and 17-21 under 35 U.S.C. 112, first paragraph.

(b) The rejection of claim 20 under 35 U.S.C. 112, second paragraph, as being indefinite.

The following rejections have been discussed in the previous office action, and are maintained for reasons of record:

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,419,953. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising hydrophilic matrix comprising 50-55% of divalproex sodium and 20-40% of hydroxypropyl methyl cellulose. The difference between the present claims and the patented claims is that the patented claims do not recite the dissolution profile instantly claimed. However, it is expected that the formulation of the patent would

have the same dissolution profile as the instant claims because both recite the same active ingredient and the hydrophilic polymer in the same amounts.

4. Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,511,678. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising hydrophilic matrix comprising 40-80% of divalproex sodium and 20-40% of the same polymers having the same dissolution profiles.

5. Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,528,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising hydrophilic matrix comprising 40-80% of divalproex sodium and 20-40% of the same polymers having the same pharmacokinetics and expected to have the same dissolution profile.

6. Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,528,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed

to treating epilepsy using formulation comprising hydrophilic matrix comprising 50-55% of divalproex sodium and 20-40% of hydroxypropyl methyl cellulose. The difference between the present claims and the patented claims is that the patented claims do not recite the dissolution profile instantly claimed. However, it is expected that the formulation of the patent would have the same dissolution profile as the instant claims because both recite the same active ingredient and the same hydrophilic polymer in the amounts.

7. Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,720,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising hydrophilic matrix comprising 40-80% of divalproex sodium and 20-50% of the same polymers having the same dissolution profiles and pharmacokinetics.

8. Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,713,086. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising hydrophilic matrix comprising 40-80% of divalproex sodium

and 20-50% of the same polymers having the same pharmacokinetics and expected to have the same dissolution profile.

Response to Arguments

9. The examiner acknowledged Applicants request to hold the double patenting rejections in abeyance until notification from the Examiner of allowable subject matter, and the examiner further acknowledged applicants' intention to file terminal disclaimers to obviate the above rejections upon receipt of allowable subject matter.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-8, 10, 12-15, and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,913,906 (906).

US '906 teaches composition for controlled release of salts of valproic acid comprising 10-80% of the active agent and polymer additive such as methyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and polyvinyl pyrrolidone, especially hydroxypropyl cellulose is preferred (abstract; col.2, lines 1-10, 63-68). The amount of the hydroxypropyl cellulose calculated to be up to 50% in the composition (col.2, lines 53-68; col.3, lines 1-3). The controlled release formulation results in sustained action of the drug with small fluctuation of the plasma level over prolonged period of time (col.1, lines 59-62). The composition is a once a day oral formulation that delivers the drug for 24 hour and shows about 97% dissolution rate profile after 24 hr. (col. 5 and 6, tables 1-4). Divalproex sodium is disclosed as one of the salts of valproic acid suitable for the formulation of the reference (col.5, lines 15-20). The reference disclosed that valproate used to treat epilepsy (col.1, line 44).

However, the reference does not explicitly teach the same dissolution profile as instantly claimed.

It is expected that the formulation of the prior art that comprises the same amount of the drug and the polymer to provide the same dissolution profile as instantly

claimed. The prior art suggested divalproex sodium and also suggests the same polymers as instantly claimed.

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to deliver once a day oral formulation comprising valproic acid salts and hydrophilic polymer as disclosed by US '906, and select the salt and the polymer that provide the sustained controlled release of the drug to provide dissolution profile according to specific patient need, motivated by the teaching of US '906 that controlled release formulation results in sustained action of the drug with small fluctuation of the plasma level over prolonged period of time, with reasonable expectation of having once a day formulation comprising divalproex sodium and hydrophilic polymer that provides sustained release of the drug with small fluctuation of the plasma level over prolonged period of time to provide dissolution profile that is best controls the patient epileptic condition.

Response to Arguments

13. Applicant's arguments filed 12/21/2007 have been fully considered but they are not persuasive. Applicants traverse the obviousness rejection over US '906 patent by arguing that the reference does not teach the same dissolution profile as the claimed invention which is a significant difference between the prior art and the claimed invention. Applicants argue that the claimed formulation exhibits significant advantages over the sustained release valproate formulations of the prior art. Specifically, the claimed formulation minimizes the variation between peak and trough plasma levels of

valproate over a 24 hour dosing period and the claimed formulation follows a zero-order release pattern thereby producing essentially flat plasma levels of valproate, once steady- state levels have been achieved. This results in a significantly lower incidence of side effects for patients who are prescribed these formulation when compared to the prior art formulations. Applicants argue that the Examiner has failed to show that one skilled in the art would have had a reasonable expectation of success based on the '906 patent of arriving at the claimed invention. Applicants submit that while it may have been "obvious to try" to make the claimed formulation based on the prior art, that the claimed invention is not obvious because making efficacious and controlled release formulations involves varying a number of different parameters as well as trying a numerous possible choices.

In response to these arguments, applicants' attention is directed to the scope of the present claims that is directed to a formulation, and all the elements of the formulation are disclosed by the prior art US '906. US '906 teaches oral formulation comprising 10-80% valproate and up to 50% hydrophilic polymer, and applicants claims are directed to the same formulation. Further, US '906 disclosed once a day formulation that shows about 97% dissolution profile after 24 hr, as desired by applicants. It is known that the dissolution of the drug is controlled by the properties of the drug itself and by the formulation in which the drug is included. Since compounds and their properties are inseparable, and since the prior art teaches the same claimed formulation, then claimed dissolution profile is expected from the prior art formulation

especially in view of the disclosure of the prior art that 97% dissolution of the drug was shown after 24 hr and sustained duration of serum valproate was obtained. It is further expected that the drug reaches 97% dissolution gradually from the time of administration till 24 hr, providing gradually increasing dissolution profile as instantly claimed. The burden is on applicants to show that the conditions of the claimed process resulted in novel and unobvious difference between the dissolution profile of the claimed formulation and the dissolution profile of the prior art formulation since the Patent Office does not have the facilities for preparing the claimed materials and comparing them with the prior art inventions. See *In re Best*, 562 F.2 1252, 195 USPQ 430 (CCPA 1977); and *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

In response to applicants argument, that no reasonable expectation of success, it is well established that the claims are given the broadest interpretation during examination. A conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969). In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of

ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

In response to applicants argument that it may have been "obvious to try" to make the claimed invention obvious, the claimed invention is not obvious, it is argued that the present claims are drawn to once a day formulation of divalproex sodium. Applicants desired to achieve valproate released at steady level over a 24-hour period. US '906 teaches the same claimed formulation resulting in sustained duration of serum level of valproate (col.4, lines 50-52). Because the properties of valproate would have been reasonably predictable at the time of the invention, there would have been a reasonable expectation of successful development of a formulation of valproate having the claimed dissolution profile as claimed. The prior art US '906 recognized the providing sustained serum rate and dissolution profile of 97% of the drug after 24 hr. Therefore, the claims were obvious because it would have been obvious to try the known formulation providing sustained serum level and dissolution profile that is 97% after 24 hr, with a reasonable expectation of successfully achieve the instantly claimed dissolution profiles.

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been *prima facie* obvious within the meaning of 35 U.S.C. 103 (a).

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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